

Amendments to the Specification

- (1) Please introduce the following *new* section heading on page 1, immediately preceding line 3:

FIELD OF THE INVENTION

- (2) Please introduce the following *new* section heading on page 1, immediately preceding line 7:

BACKGROUND OF THE INVENTION

- (3) Please introduce the following *new* section heading on page 2, immediately preceding line 23:

SUMMARY OF THE INVENTION

- (4) Please introduce the following *new* section headings and paragraphs on page 6, immediately preceding line 16:

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in more detail with the aid of the following Figures and Examples.

Figures 1A-B show, respectively, the cDNA and amino acid sequences (SEQ ID NOS: 1 and 2, respectively) of human GMCSF, taken from Genbank Accession No. NM_000758.

Figure 2 is a graph showing the effect of PGE and GMCSF on gene expression in U937 cells. Cells were treated for 4 hours with PGE₂, with and without GMCSF, washed to remove the treatment, and incubated for a further 20 hours before the cells were pelleted and RNA extracted. The mRNA levels of CD14, CD80, CD86, BCL-2, BAX, COX-1 (cyclo-oxygenase 1), COX-2, PGES (prostaglandin synthase), EP2 (a prostaglandin receptor), EP4 (a prostaglandin receptor), PDE4B (a phosphodiesterase), IRAK-IV, CIITA (MHC class II transactivator), MHC-II, IL-10 and granulysin (abbreviated to granlin), were measured. The graph indicates the percentage change in expression levels in the presence of GMCSF and PGE₂.

Figure 3 is a graph showing the synergistic effect of PGE and GMCSF on the production of IL-10 mRNA in U937 cells, and that this phenotype is maintained 48 hours after removal of the treatment. Cells were treated for 4 hours with the agents indicated below the graph, washed to remove the treatment, and incubated for a further 48 hours before the cells were pelleted and RNA extracted. PGE2, E2 and E all refer to prostaglandin E2 ; GM refers to GMCSF; and M refers to MCSF.

Figure 4 is a graph showing the synergistic effect of PGE and GMCSF on the release of IL-10 protein in U937 cells, and that this phenotype is maintained after removal of the treatment. Cells were treated for 4 hours with the agents indicated below the graph, washed to remove the treatment, and incubated for a further 20 hours before the medium was assayed for IL-10. PGE refers to prostaglandin E2, and GM refers to GMCSF.

Figure 5 is a diagram showing agents which control intracellular cAMP. Open arrows are effectively lowering intracellular cAMP levels. Solid arrow is stimulation. Combinations will be synergistic.

Figure 6 shows the relative efficacy of various agents in inducing IL-10 expression. See Example 4 for details.

Figure 7 shows the relative efficacy of various agents in inducing IL-10, expressed as a ratio of IL-10/TNF α mRNA expression. See Example 5 for details.

Figure 8 shows the relative efficacy of various agents and combinations of agents in inducing granulysin mRNA expression. See Example 6 for details.

Figure 9 shows that there is a synergistic effect between a prostaglandin (PGE2) and GMCSF and probenidol on the expression of IL-10.

DETAILED DESCRIPTION OF THE INVENTION

- (5) Please replace the paragraph beginning on page 34, line 19, with the following amended paragraph:

The invention includes the administration of an agent which raises the effective cAMP concentration in a monocyte cell and/or GM-CSF or derivative thereof and/or an antigen or derivative thereof to a mucosal site remote from the site of inflammation *eg* they could be co-administered as a suppository in the case of arthritis. This embodiment may be particularly advantageous as pathologic changes in the gastrointestinal tract may be associated with clinical complaints in multiple organs, including the musculoskeletal system (Alghafeer & Sigal, *Bulletin on the Rheumatic Diseases*, 51 (2), available online from arthritis.org website: http://www.arthritis.org/research/bulletin/vol51-no2/51_2_printable.asp, incorporated herein by reference). Some reactive arthritis can be triggered by inflammatory bowel diseases, and lymphocytes from the gut mucosa have been reported to migrate to joint tissue in enteropathic arthritis (Salmi & Jalkanen (2001) *J Immunol.*, 166 (7): 4650-7, incorporated herein by reference).

- (6) Please delete the paragraphs appearing at page 54, line 19 through page 56, line 16.

- (7) Please replace the listing of probes and primers spanning page 59, line 10 to page 62, line 14 with the revised listing below:

IL-10 primers

CTACGGCGCTGTCATCGAT (SEQ ID NO: 3)

TGGAGCTTATTAAAGGCATTCTTCA (SEQ ID NO: 4)

IL-10 probe

CTTCCCTGTGAAAACAAGAGCAAGGCC (SEQ ID NO: 5)

BAX primers

CATGGAGCTGCAGAGGATGA (SEQ ID NO: 6)

CTGCCACTCGGAAAAAGACCT (SEQ ID NO: 7)

Bax Probe

TGCCGCCGTGGACACAGACTCC (SEQ ID NO: 8)

BCL2 primers

CCGGGAGGCGACCGTAGT (SEQ ID NO: 9)

GGGCTGCGCACCTTTC (SEQ ID NO: 10)

BCL2 probe

CGCCGCGCAGGACCAGGA (SEQ ID NO: 11)

CD80 primers

TCCACGTGACCAAGGAAGTG (SEQ ID NO: 12)

CCAGCTCTTCAACAGAAACATTGT (SEQ ID NO: 13)

CD80 Probe

AAGAAGTGGCAACGCTGTCCTGTGG (SEQ ID NO: 14)

CD86 primers

CAGACCTGCCATGCCAATT (SEQ ID NO: 15)

TTCCTGGTCCTGCCAAAATACTA (SEQ ID NO: 16)

CD86 Probe

CAAACCTCTCAAAACCAAAGCCTGAGTGAGC (SEQ ID NO: 17)

COX-1 primers

TGTTTCGGTGTCCAGTTCCAATA (SEQ ID NO: 18)

ACCTTGAAGGAGTCAGGCATGAG (SEQ ID NO: 19)

COX-1 Probe

CGCAACCGCATTGCCATGGAGT (SEQ ID NO: 20)

COX-2 primers

GTGTTGACATCCAGATCACATTTGA (SEQ ID NO: 21)

GAGAAGGCTTCCCAGCTTTTGTA (SEQ ID NO: 22)

COX-2 Probe

TGACAGTCCACCAACTTACAATGCTGACTATGG (SEQ ID NO: 23)

EP2 primers

GAC CGC TTA CCT GCA GCT GTA C (SEQ ID NO: 24)

TGA AGT TGC AGG CGA GCA (SEQ ID NO: 25)

EP2 Probe

CCA CCC TGC TGC TGC TTC TCA TTG TCT (SEQ ID NO: 26)

EP4 primers

ACGCCGCCTACTCCTACATG (SEQ ID NO: 27)

AGAGGACGGTGGCGAGAAT (SEQ ID NO: 28)

EP4 Probe

ACG CGG GCT TCA GCT CCT TCC T (SEQ ID NO: 29)

PDE4b primers

CCTTCAGTAGCACCGGAATCA (SEQ ID NO: 30)

CAAACAAACACACAGGCATGTAGTT (SEQ ID NO: 31)

PDE4b Probe

AGCCTGCAGCCGCTCCAGCC (SEQ ID NO: 32)

Granulysin primers

CAGGGTGTGAAAGGCATCTCA (SEQ ID NO: 33)

GGAGCATGGCTGCAAGGA (SEQ ID NO: 34)

Granulysin Probe

CGGCTGCCCCACCATGGC (SEQ ID NO: 35)

CD 14 primers

GCGTCCGAGATGCATGT (SEQ ID NO: 36)

AGCCCAGCGAACGACAGA (SEQ ID NO: 37)

CD 14 Probe

TCCAGCGCCCTGAACTCCCTCA (SEQ ID NO: 38)

E synthase primers

CGGAGGCCCCCAGTATTG (SEQ ID NO: 39)

GGGTAGATGGTCTCCATGTCGTT (SEQ ID NO: 40)

E synthase Probe

CGACCCCGACGTGGAACGCT (SEQ ID NO: 41)

IRAKM primers

CCT GCC CTC GGA ATT TCT CT (SEQ ID NO: 42)

CTT TGC CCG CGT TGC A (SEQ ID NO: 43)

IRAKM probe

CAC ACC GGC CTG CCA AAC AGA A (SEQ ID NO: 44)

CIITA primers

GCTGTTGTGTGACATGGAAGGT (SEQ ID NO: 45)

RTGGGAGTCCTGGAAGACATACTG (SEQ ID NO: 46)

CIITA Probe

CCGCGATATTGGCATAAGCCTCCCT (SEQ ID NO: 47)

Class II primers

AGCCCAACGTCCTCATCTGT (SEQ ID NO: 48)

TCGAAGCCACGTGACATTGA (SEQ ID NO: 49)

Class II ~~Class II~~ Probe

TCATCGACAAGTTCACCCACCAAGTG (SEQ ID NO: 50)

- (8) Please replace the listing of probes and primers at page 64, lines 17-21 as follows:

IL-10 primers

CTACGGCGCTGTCATCGAT (SEQ ID NO: 3)

TGGAGCTTATTAAAGGCATTCTTCA (SEQ ID NO: 4)

IL-10 probe

CTTCCCTGTGAAAACAAGAGCAAGGCC (SEQ ID NO: 5)

- (9) Please replace the listing of probes and primers on page 65, lines 8-13 as follows:

TNF α Primers

GGAGAAGGGTGACCGACTCA (SEQ ID NO: 51)

TGCCCAGACTCGGCAAAG (SEQ ID NO: 52)

TNF α probe

CGCTGAGATCAATCGGCCCGACTA (SEQ ID NO: 53)

- (10) Please amend the specification to include the accompanying Sequence Listing.